UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,597	09/25/2003	Alexa L. Martinez	2057.0040002	1312

26111 7590 03/25/2009

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
GUPTA, ANISH	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
03/25/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/669,597	MARTINEZ ET AL.	
	Examiner	Art Unit	
	ANISH GUPTA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. The amendment, filed 11-20-07, is acknowledged. Claims 1-2, 21, 27-31, 59, 60, 77-80, 82-86, 102-104 and 106-108 were amended, claims 22 was canceled, and claim 109 was added.

2. Applicant's election of Group I, with the species of GM-CSF, dihydroxy poly(ethylene glycol) in the reply filed on March 7, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicants state that claims 1-11, 13-15, 17-27, 30, 35, 38, 59-67, 69-71, 73-82, 85, 90, 93-96, 101-108 and newly added claim 109 read on the elected species. Claims 12,16,28,29,31-34,36,37,68,72,83,84,86-89,91 and 92, 97-100 are withdrawn from consideration as corresponding to non elected species.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-11, 13-15, 17-27, 30, 35, 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "[a] conjugate comprising one or more bioactive components" and "polyalkylene glycol is attached to a single bioactive component at a single site on the polyalkylene

glycol." It is unclear how more than one bioactive components can be present in the conjugate when the claim recites that the PEG is attached to a single bioactive component.

Applicants arguments

Applicants argue that the claims have been amended to recite that each polyalkylene glycol is attached to one of the bioactive components.

Applicants arguments have been fully considered but have not been found persuasive.

The claim recites "A conjugate." Thus, the claim is drawn to a single compound and not composition comprising multitude of compounds. Thus, a claim which requires that that the components be attached to a single site and which recites "A conjugate" is inconsistent when it also recites "one or more bioactive components" and "each said polyalkylene glycol." The claim is still indefinite.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 1-11, 13-15, 17-27, 30, 35, 38, 59-67, 69-71, 73-82, 85, 90, 93-96, 101-109 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of

California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to conjugates comprising one or more bioactive component covalently attached to a linear or branched polyalkylene glycol. The base claim does not define the bioactive agent and subsequent dependent claims 27-31, while claiming specific biological agents, also claims mimic or functional agonist of any of the specific peptides/proteins claimed. The generic statement of biologically active agent or mimic of functional antagonist, does not provide ample written description for the compounds since the claims do not describe a singe structural feature. The specification does provide examples of what qualify as compounds of the claimed invention. The specification describes, specifically, non-peptide agents such as, daunorubicin, doxorubicin, p-aminoaniline mustard, melphalan, cytosine arabinoside ("Ara-C") and other anti-metabolic compounds, e.g., gemcitabine, amphotericin B and peptides such as hemoglobin, Factors VII, VIII, and IX, immunoglobulins, insulin, IL-1 through IL-18, interferons, colony stimulating factors including without limitation GM-CSF, G-CSF, macrophage colony

stimulating factor, thrombopoietin, megakaryocyte growth and development factor, erythropoietin, platelet derived growth factor, phospholipase-activating protein ("PLAP"), leukemia inhibitory factor ("LIF," also known in the art as "Steel Factor"), neurotrophic factors, insulin, lectins and ricins, tumor necrosis factors and related proteins, TGF-alpha or TGF-beta, fibroblast growth factors, epidermal growth factors, hepatocyte growth factors, hormones, somatomedins, erythropoietin, prolactin, chorionic gonadotropin, follicle-stimulating hormone, thyroid-stimulating hormone, prolactin, tissue plasminogen activator (see page 28 of the specification). The MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. However, the specific peptide/non-peptide bioactive agents do not provide written description for all of the bioactive agents, mimetic, and functional antagonist of the claimed invention. The possible structural variations are limitless to any class of bioactive compound. The specification does not provide description for bioactive agents that include different types of heterocycles, PNA molecule with divergent DNA sequences, etc… The specification does not disclose s single mimetic of any of the peptides/non-peptide molecules disclosed, nor does the specification provide any specific illustrations of funcational antagonist. It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus. The specification is limited to the above mention cyclic molecules that share a common core. There is no disclosure of a polymer with hydrogen bonding sites and capable of promoting release of the active compounds does not provides sufficient structural characteristics.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Response to Arguments

Applicants argue that written description requirement must be viewed in light of the state of the art at the time of filing. At the time of filing, the level of knowledge in the art of PEGylation technology was very high. "The ordinary skilled artisan would have readily understood, based on the present specification viewed in the context of knowledge available at the time of filing of the present application, that any and all peptide/non-peptide bioactive agents, as well as muteins, mimetics, antagonist, variants, analogs and derivatives thereof, could be utilized in the practice of the presently claimed invention." The specification exemplifies several polyalkylene oxide-conjugated bioactive agents. Furthermore, "Applicants respectfully submit that these requirements [physical structure and/or chemical properties] have meent met in the present specification, as the structure, chemical properties, and functional characteristics of the recited protein/non-protein bioactive agents were all well known at the time of filing, in the same way as the DNA sequences used to make chimeric genes were known in Capon."

Applicants arguments have been fully considered but have not been found persuasive.

First, regarding Applicants reference to pegylation technology, it is unclear how pegylation technology can be used to provide written description for the claimed invention. The claims require the presence of hydroxyl group on every distal end of the polyalkylene glycol. Known pegylation

technology does not have a hydroxyl group on every distal end of the glycol. Rather, the PEG groups in conventional pegylation have at least one protected hydroxy, in the form of methoxy-PEG. It is unclear how the disclosure of methoxy-PEG technology can be used to provide written description PEG diols in pegylation. Note that that the enablement rejection sets forth problems associated with PEG diols in pegylation chemistry. Applicants state that the specification provides examples. However, Applicants only make reference to methoxy-PEG. The claims require that the PEG used have a distal hydroxyl at each terminus. Finally, the MPEP states a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. See MPEP 2105. Thus, the mere disclosure of different biological agents do not provide written description for the conjugate because the list would not "reasonably lead" those skilled in the art to any particular species claimed.

The rejection is maintained.

Enablement

5. Claim 1-11, 13-15, 17-27, 30, 35, 38, 59-67, 69-71, 73-82, 85, 90, 93-96, 101-109 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the

breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) the nature of the invention

The invention is drawn to methods for preparing conjugate that have reduced anigenticity and immunogenicity compared to similar conjugates prepared using PEG containing methoxyl or another alkoxy group.

(2) the state of the prior art

The art states that one of the hydroxyl groups of the PEG is converted to mono-functional methoxy-PEG since high diol concentration will yield unwanted cross-linking conjugates (see page 406 of Veronese). Monfuncationality of methoxyPEG makes it particularly suitable for protein and peptide modification because it yields reactive PEGs that do not produce crosslinked polypeptides, as long as diol PEG has been removed (see page 462 of Roberts). Roberts states that a promising strategy for generating heterobifuncational PEGs and using them in polymerization. The art has recognized PEG groups with a hydroxyl group at one terminus and amino group at the other end or PEG groups with formyl group on one end and hydroxyl group at the other end. However, Roberts states that "This strategy also has its limits. Only those anions that are desirable as end groups and suitable for initiating polymerization are useful for synthesis of heterobifunctional PEG by this route. This method is also limited by the fact that rigorous exclusion of water is necessary to

prevent the formation of the diol. This problem becomes more sever as the PEG molecular weight increase." (See page 472-473).

(3) the relative skill of those in the art;

The skill in the art is high.

(4) the predictability or unpredictability of the art

Given the state of the art with respect diol and crosslinking, it is highly unpredictable to form a PEG conjugate with one biological agent.

(5) the breadth of the claims

The claims are drawn to a product where the conjugate comprises one or more bioactive components covalently attached to a polyalkylene glycol, wherein the glycol does not comprise an alkoxy group. Applicants elected the bioactive component as GM-CSF and the polyalkylene glycol as dihydroxy PEG. Claim 59 require the product to be obtained by using modifying one end of the glycol with a "derivatizing group" and the other end being a hydroxyl group. Thus, a PEG with a free hydroxyl end is utilized in the formation of the conjugation.

(6) the amount of direction or guidance presented and (7) the presence or absence of working examples

The specification provides for general conditions on how to conjugate PEG to a boactive agent. The specification states that the bioactive agent can be reacted with dihydroxyPEG in an "aqueous reaction medium that can be buffered, depending on the pH requirements of the

nucleophile and the activated polymer. . . The optimal reaction condition necessary to maintain the stability of the bioactive component, the reaction efficiency, etc.., are within the level of the ordinary skill in the art." The specification also provide working examples that that test for antibodies to monomethoxyPEG and examples that illustrate antibodies with PEGs lacking methoxyl groups. Other working example illustrate the synthesis of the α-hydroxy-β monnitrophenyl carbonate PEG and α-hydroxy-β monopropionaldehyde PEG. The specification, however, does not provide any examples that demonstrate the coupling of a hetrobifuncational PEG, with a free hydroxyl group, to a protein, especially GM-CSF. Such guidance is necessary because the art indicates that the strategy utilizing hetrobifuncatioal PEG, that have a free hydroxyl group, also has its limits. Only those anions that are desirable as end groups and suitable for initiating polymerization are useful for synthesis of heterobifunctional PEG by this route. This method is also limited by the fact that rigorous exclusion of water is necessary to prevent the formation of the diol. This problem becomes more sever as the PEG molecular weight increase. Further, the art recognizes that when PEG-diol is present, unwanted crosslinking occurs. The specification does not provide guidance as to how to exclude water to prevent the formation of diol. Note that the claims require that the PAG is attached to a single bioactive component at a single site on the PEG. This claim language seemingly excludes crosslinked proteins. However, without protection of the free hydroxyl or how to prevent formation of diol, a crosslinked product would occur.

(8) the quantity of experimentation necessary.

Given the problems associated with conjugation of PEG-diols to bioactive agents, one would be burdened with undue experimentation to make the claimed invention.

Response to Arguments

Applicants argue that the instant application disclose the use of PEG conjugation under aqueous condition. Thus, the prior art condition are not applicable to the claimed invention. Applicants assert that the suitable method for polyalkylene glycol polymerization and protein conjugation were well known to those of ordinary skill in the art at the time of filing of the present invention. "As understood by one of ordinary skill in the art, the presently claims are directed to monofunctionally active polyakylene polymer (e.g. those that are readily conjugated to bioactive agents under aqueous conditions as described in the specification.) Thus, the problematic issue of unwanted crosslinking cannot occur to any significant extent."

Applicants arguments have been fully considered but have not been found persuasive.

While Applicants arguments provide a detail analysis as to the law regarding the standards of enablement, they do very little in the way of resolving the issue regarding enablement. Applicants assert that one of ordinary skill in the art can look the state of the art of polyalkylene conjugation. However, as stated above, it is unclear how the state of the art can be of assistance when the claimed invention use PEG diols that have, unlike applicants assertions, two hydroxyl functionalities prior to conjugation to the bioactive molecule. Again the prior art attempts to avoid the use of diols in aqueous reaction systems because of unwanted crosslinking reactions. For this reason, the prior art utilizes non-aqueous reaction systems. Here the specification calls for aqueous reaction systems that use PEG diols. Given the art, one would expect unwanted crosslinking reactions to occur. Applicants make reference to example 5 in the specification. However, the examples describe the preparation of PharmaPEG-mononitrophenyl carbonate and not the a conjugation of PEG diols to a bioactive molecule. Further the reaction system in example 5 utilizes an organic solvent in acetonitrile. Example 6, disclose the synthesis of PharmaPEG-monoaldehyde from a PEG Diol, again using organic solvents such as toluene. The specification does not provide any examples that

demonstrate the coupling of a hetrobifuncational PEG, with a free hydroxyl group, to a protein, especially GM-CSF. The art recognizes that when PEG-diol is present, unwanted crosslinking occurs. The specification does not provide guidance as to how to exclude water to prevent the formation of diol. Note that the claims require that the PAG is attached to a single bioactive component at a single site on the PEG. This claim language seemingly excludes crosslinked proteins. However, without protection of the free hydroxyl or how to prevent formation of diol, a crosslinked product would occur.

Rejection maintained.

6. The rejection of claims 1-11, 13-15, 17-27, 30, 35, 38, 94-95, rejected under 35 U.S.C. 102(b) as being anticipated by Kohno et al. is hereby withdrawn.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (571)272-0965. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can normally be reached on (571) 272-0562. The fax phone number of this group is (571)-273-8300.

/Anish Gupta/
Primary Examiner, Art Unit 1654